IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Jeffrey R. Dahlen, et al.

Title: USE OF B-TYPE NATRIURETIC PEPTIDE AS A PROGNOSTIC INDICATOR IN ACUTE CORONARY SYNDROMES

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CERTIFICATE OF MAILING
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10/25/06
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DECLARATION OF DR. NORMAN ALAN PARADIS

I, Norman Alan Paradis, M.D., state and declare as follows:

1. I am currently Vice President of Clinical Medical Affairs for Biosite Incorporated, San Diego, CA, assignee of the above-referenced Dahlen *et al.* patent application. I am also a Visiting Professor of Surgery and Attending Physician at the University of Colorado Health Sciences Center, Denver Colorado. I received my medical degree from Northwestern University Medical School in 1984, and have been employed as a physician since that time. I have specialty training in Emergency Medicine, and have been a Fellow of the American Academy of Emergency Medicine since 1990. A copy of my *curriculum vitae* is attached to this declaration. I have read and am familiar with the above-referenced Dahlen *et al.* patent application and the Office Action dated July 27, 2006.

2. I have been asked to comment regarding the whether or not the discovery that BNP measurements (and measurement of BNP-related polypeptides such as NT-proBNP) provide independent prognostic information vis-à-vis "traditional" cardiac necrosis markers such as cardiac troponin across the full spectrum of acute coronary syndromes was unexpected at the

time the above-referenced Dahlen *et al.* patent application was filed, and whether that discovery is of practical significance.

3. I conclude that the independence of these measurements was important and unexpected, and of substantial practical experience. For convenience, I will refer to "BNP measurement" in the following comments, but these comments should be considered equally applicable to the measurement of BNP-related polypeptides such as NT-proBNP.

4. That the data in the present application demonstrating that BNP measurements are independent of cardiac necrosis markers such as cardiac troponin for prognosis is demonstrated by de Lemos *et al.*, *N. Engl. J. Med.* 345: 1014-21 (2001) (hereinafter "the deLemos *NEJM* paper"). The *NEJM* is considered by those of skill in the art to be perhaps the preeminent journal in the medical field, and publication in the *NEJM* is considered to be reserved for discoveries of the highest novelty and importance. I understand that the authors of the deLemos *NEJM* paper are investigators from the multicenter "TIMI-16" cardiovascular study that served as the source of samples for the examples in the patent application.

5. The surprising nature of the discovery that BNP as a prognostic marker is independent of what are considered "traditional" markers of cardiac necrosis such as cardiac troponins comes from a review of the scientific literature. With regard to cardiac troponin, Antman *et al.*, *N. Engl. J. Med.* 335: 1342-49, 1996 on page 1348, right column, states that cardiac troponin increases "presumably because the amount of myocardial necrosis increases." As for BNP, Hassan and co-workers reported in *Médecine Nucléaire* 24: 301-10, 2000, on the use of thallium-201 single photon emission computerized tomography (Tl-201 SPECT) to distinguish subjects having necrotic myocardium from subjects having ischemic myocardium. Hassan *et al.* then compared plasma BNP concentrations in these two groups, concluding that, while BNP was significantly increased in the case of cardiac necrosis, BNP did not increase due to cardiac ischemia. This would lead the skilled artisan to believe that BNP, like cardiac troponins, increases "presumably because the amount of myocardial necrosis increases." Thus, the skilled artisan would conclude that BNP would provide similar information to other necrosis markers such as troponin. The evidence provided in the present specification that this is not the case, then, was quite surprising.

6. Confirmation for my conclusion of the surprising nature of this discovery is provided by an editorial authored by the cardiologist LeRoy Rabbani, *N. Engl. J. Med.* 345: 1057-59 (2001), which was published in the same issue of the *NEJM* as the de Lemos *et al.* *NEJM* publication. The editorial discussed the de Lemos *et al.* article and specifically emphasized the importance of the discovery being reported (emphasis added):

> "[a] single measurement of B-type natriuretic peptide... predicted the risk of death in patients who had myocardial infarction with ST-segment elevation, myocardial infarction without ST-segment elevation, or unstable angina.... Moreover, the relation between the long-term risk of death and the B-type natriuretic peptide level was independent of electrocardiographic changes, troponin I levels, renal function, and the presence or absence of clinical evidence of congestive heart failure. Furthermore, even in patients who had unstable angina and no evidence of myocyte necrosis on the basis of the absence of an elevation in troponin I levels, an elevation in B-type natriuretic peptide levels portended a worse prognosis.

It is my understanding that companion editorials are generally reserved for extremely important findings. In addition, the *NEJM* editorial was authored by LeRoy Rabbani, an Associate Professor of Clinical Medicine at Columbia University, a highly experienced interventional cardiologist with over 20 years experience including an extensive bibliography (listed as an author on 47 articles in Medline). The fact that the de Lemos *et al. NEJM* article was accepted for publication, coupled with the companion *NEJM* editorial, is strong evidence that the findings in de Lemos are new and profound.

7. To understand the importance and unexpected nature of the discovery that BNP measurements provide independent prognostic information across the full spectrum of acute coronary syndromes ("ACS"), it is necessary to first understand the definition of "ACS," and the differences between myocardial infarction and myocardial ischemia. The term "acute coronary syndromes" is used as an umbrella term to refer to a spectrum of diseases – unstable angina ("UA"), non-ST-segment elevation myocardial infarction (NSTEMI), and myocardial infarction with ST-segment elevation (STEMI). Unstable angina refers generally to myocardial ischemia that causes pain at rest. In UA, the blockage of the affected artery does not completely block blood supply to the myocardium, and is not generally thought to result in the myocardial necrosis characteristic of myocardial infarction. Myocardial infarction, on the other hand, differs in that the blockage of the affected artery is sufficient to cause necrosis (that is, death) of myocardial

cells. *See, e.g.*, Alpert *et al., J. Am. Coll. Cardiol.* 36: 959-69, page 960, section entitled "II. Clinical Presentation" ("It is accepted that the term MI reflects a loss of cardiac myocytes (necrosis) caused by prolonged ischemia").

8. As discussed above, the Hassan *et al. Médecine Nucléaire* publication would lead the skilled artisan to believe that BNP, like cardiac troponins, increases "presumably because the amount of myocardial necrosis increases." Thus, it is plain that the skilled artisan would not have been led to believe that BNP would be a prognostic marker outside the context of myocardial infarction. Confirmation of the unexpected nature is provided by the fact that, once the relationship between BNP was discovered, it was published by the *New England Journal of Medicine*. Again, it is my understanding that publication in the *NEJM* is considered to be reserved for discoveries of the highest importance. And the import of the publication was such that the *NEJM* also elected to publish an accompanying editorial by the cardiologist LeRoy Rabbani, which highlighted the importance of the finding that "even in patients who had unstable angina and no evidence of myocyte necrosis on the basis of the absence of an elevation in troponin I levels, an elevation in B-type natriuretic peptide levels portended a worse prognosis."

9. Given the state of the art at the time the above-referenced Dahlen *et al.* patent application was filed, it is my conclusion that it was surprising and unexpected that BNP would be an independent prognostic marker relative to "traditional" cardiac necrosis markers like troponin. It was likewise surprising and unexpected that BNP would prove to be a prognostic marker across the entire spectrum acute coronary syndromes.

10. The practical result of the discovery is immediately apparent to those of skill in the art. That is, independent prognostic markers provide for improved patient risk stratification by providing complementary information to one another. Sabatine and his co-authors in *Circulation* 105: 1760-63, 2002, reports on the use of BNP, cardiac troponin I, and an inflammatory marker (C-reactive protein, or CRP) in a "multimarker strategy" for risk stratification of ACS patients. As the authors demonstrate, each of these markers can provide unique prognostic information in patients with ACS. The authors conclude that "[a] simple multimarker strategy that categorizes patients based on the number of elevated biomarkers at presentation allows risk stratification over a broad range of short- and long-term major cardiac

events." Sabatine *et al.*, Abstract. This practical advantage has been widely recognized, acknowledged, and adopted in the art, as demonstrated by the following excerpt from Silver *et al.*, "BNP Consensus Panel 2004: A Clinical Approach for the Diagnostic, Prognostic, Screening, Treatment Monitoring, and Therapeutic Roles of Natriuretic Peptides in Cardiovascular Disease," *CHF* 10[5 Suppl. 3]: 1-30 (2004). In this report, prepared by "an expert panel... gathered by selecting clinicians and scientists with expertise with the natriuretic peptide system," the practical advantage of combined measurements of BNP and cardiac troponin is made clear:

> 7.2 When used together in a combined strategy, BNP and cardiac troponin provide a more effective tool for identifying patients at increased risk for clinically important cardiac events related to HF and acute coronary syndrome. Multimarker panels that include BNP troponin, and C-reactive protein are now available and each of these markers provides unique and independent information with regard to patient outcomes.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements are so made punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Oct 18, 2006
Date

Norman Alan Paradis, M.D.